INTRODUCTION

Cardiovascular diseases (CVDs) are among the leading causes of death all over the world, despite modern therapeutic advances. Atherosclerosis – a progressive disease characterized by accumulation of lipids and fibrous elements in the large arteries – constitutes one of the most important contributor to this growing burden of CVDs ***(Libby, 2002; Yuksel et al., 2015)***.

In Egypt, it was proven that coronary artery diseases are the main cause of sudden cardiac death in Egyptian population; even it may be the first and only symptom ***(Hassan, 2003).***

Atherosclerosis begins early in life. The pathological process that underlies this disease is arterial wall thickening due to the formation of atherosclerotic plaque**.** It is considered to be a multi-factorial disease with numerous risk factors including: smoking, alcohol abuse, hypertension, diabetes mellitus, dyslipidemia, and infection with some micro-organisms. All these factors involve complex interactions between the pathways; associated with lipid metabolism, coagulation, hypoxia, apoptosis, inflammation and the immune response ***(Modifi et al., 2008).***

The traditional view of atherosclerosis, as a blind lipid storage disease, is analogous to the build-up of rust in a water pipe. This crumbles in the face of extensive and growing

evidence that inflammation participates centrally in all stages of this disease, from the initial lesion to the end stage thrombotic complications ***(Libby, 2006).***

Over the past years, a prominent role of inflammation in atherosclerosis has garnered an increased interest. The recruitment of inflammatory cells in atherosclerotic lesions is a constitutive phenomenon throughout the process of lesion initiation and plaque growth ***(Hansson, 2005)***.

Normally, endothelial cells which form the inner most surface of the arterial wall resist the adhesion by leukocytes. However, triggers or risk factors of atherosclerosis can initiate the expression of cellular adhesion molecules by endothelial cells, thus allowing the attachment of leukocytes to the arterial wall ***(Libby, 2006).***

Cellular adhesion molecules include selectins, integrins and immunoglobulin gene super family. One of the members of the immunoglobulin gene super family is *CD106* or *Vascular Cell Adhesion Molecule-1 (VCAM-1)*. This molecule serves as an endothelial ligand for the integrins expressed on the leukocytes (monocytes and T-lymphocytes) and platelets, mediating their tight attachment to the endothelium and subsequent trans-endothelial migration of leukocytes ***(Martin-Ventura et al., 2009)***.

Once in the arterial intima, the monocytes continue to undergo inflammatory changes, transform into macrophage, engulf lipids, and become foam cells. Also, T-lymphocytes migrate into the intima, where they release pro-inflammatory cytokines that amplify the inflammatory activity ***(Libby, 2006)***.

Atherosclerotic plaques are subjected to angiogenesis (formation of new blood vessels from a pre-existing vascular network) to supply the viable cells within the plaque with oxygen ***(Chen and Walterscheid, 2006)***. Some studies strengthened the concept that the intra-plaque neo-vascularization could play a major role in plaque progression and leukocyte infiltration, and may also serve as a measure of risk for the development of future events ***(Michel et al., 2011)***.

CD105 or Endoglin is a homodynamic integral membrane glycoprotein. It is a component of the transforming growth factor-B receptor complex. It is predominantly expressed in angiogenic endothelial cells and is up-regulated during hypoxia. It is a sensitive marker for identification of neo-vascularization, growth and prediction of tumour outcome ***(Marioni et al., 2008).***

Angiogenesis and inflammation can be independent processes, but are closely related in some biologic processes. In acute inflammation, microvessels dilate and increase their permeabitity. In chronic inflammation, angiogenesis is the

prominent vascular response and may function to sustain inflammation ***(Folkman, 1995)***.

Some studies have shown a close association between areas of neo-vascularization and accumulation of inflammatory cells, in atherosclerotic segments, indicating ongoing inflammatory reactions and leaky microvessels. This association was shown to be prominent in patients with symptomatic atherosclerosis and in the shoulder regions of the plaques, which are known to be prone to rupture ***(Dunmore et al., 2007).***

Aim of the Work

The aim of our work is to study and assess the expression of **CD106** (Vascular cell Adhesion Molecule-1 / VCAM-1) and **CD105** (Endoglin) in variable atherosclerotic plaques of human coronary arteries in order to correlate its relationship with progression of atherosclerotic plaques and/or sudden death.

.

Chapter 1
ANATOMICAL BACKGROUND

The heart is a hollow muscular organ responsible for blood circulation. This highly specialized muscle is marvelously organized into an integrated unit capable of moving 45 million gallons of blood through one billion pumping circles during a normal lifetime. From the moment it begins beating until time it stops, the human heart works tirdlessly ***(Mc Vay, 1984; Taber et al., 2009).***

Site, size and weight of the heart:

The heart is placed in the middle mediastinum assuming an oblique position. The size of a person's heart is about that of his/her fist. An average adult heart measures about 12 cm long, 8-9 cm at its widest point and 6 cm thick**.** The heart weight varies according to sex and age. Its mass is approximately 0.45% of the total body mass in males (280-340 gm) and approximately 0.4% of the total body mass in females (230-280 gm) ***(Mill et al., 2003).***

Chambers, septa and valves of the heart: *(Figure 1)*

The heart consists of four well separated chambers, two superior atria (separated by inter-atrial septum) and two inferior ventricles (separated by inter-ventricular septum) ***(MacDonald and Mathew, 2009; Wikipedia, 2013).***

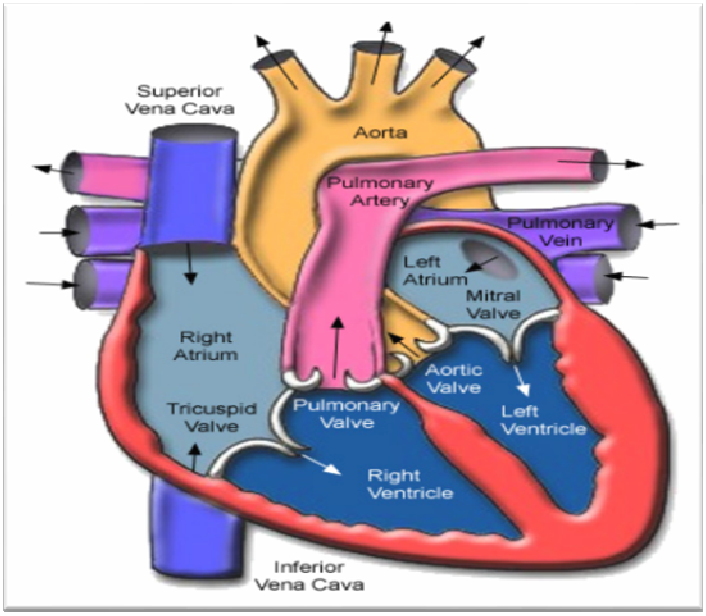

Figure (1): Chambers, septa and valves of the heart ***(Wikipedia, 2013).***

Attached to the rings between the atria and the ventricles are the atrio-ventricular valves: the right is the *tricuspid valve* while the left is the *mitral (bicuspid) valve*. The *aortic* and the *pulmonary valves* are attached to the rings at the bases of the aortic and pulmonary arteries respectively ***(John, 2006)***.

Blood supply of the heart:

- ***Coronary Arteries: (Figure 2)***

The coronary arteries are the network of blood vessels that carry oxygen and nutrient-rich blood to the cardiac muscle tissue. They branch off from the major artery of the heart – the *aorta*. There are 2 main coronary arteries, namely the *right* and *left* coronary arteries. Each coronary artery gives off a number

of branches that supply the entire heart ***(Gray, 2004; Taber et al., 2009).***

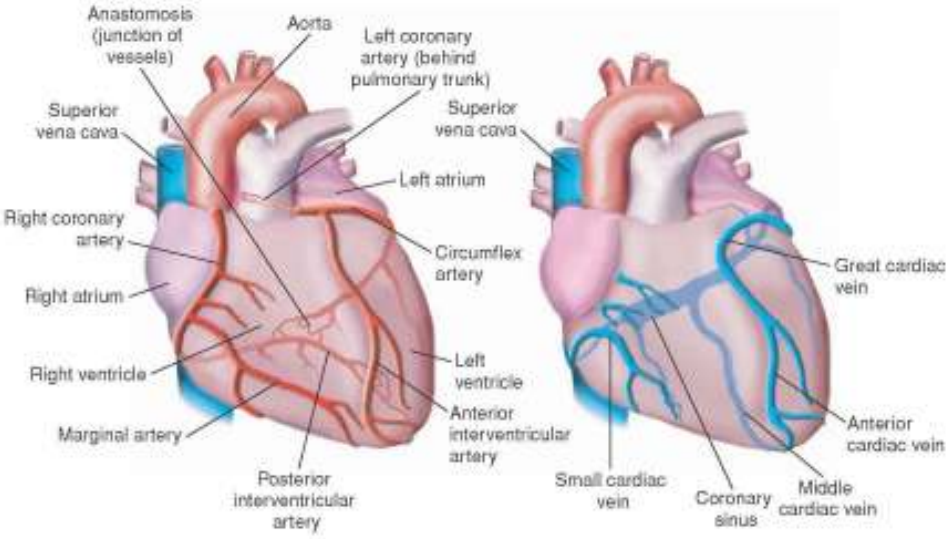

Figure (2): Coronary arteries ***(Sara, 2015).***

1. Right coronary artery (R):

It arises from the aorta, courses through the right atrio-ventricular groove then curves posteriorly and continues downwards. It supplies the whole of the right ventricle (except for a very small region), a variable part of the diaphragmatic aspect of the left ventricle, the posterior-inferior third of the inter-ventricular septum and part of conducting system. In 65% of people, it gives a posterior descending branch which supplies the inferior wall of left ventricle and inferior part of septum ***(John, 2006)***.

2. Left coronary artery:

It arises from the aorta, passes between the pulmonary trunk and left atrial appendage. It divides into 2 branches: *left anterior descending* branch (AD) and left *circumflex* branch (C)**.** In 15% of cases a 3rd branch arises between these 2 branches known as the *ramus intermedius* or *intermediate* branch **(John, 2006)**.

- Left anterior descending artery (AD):

It appears to be a direct continuation of the left main coronary artery which descends into the anterior inter-ventricular groove and continues up to the apex of the heart. It gives septal and diagonal branches which supply the most of the inter-ventricular septum; which also supply anterior, lateral, apical wall of the left ventricle and anterior papillary muscle of the mitral valve.

- Left circumflex artery (C):

It branches from the left main coronary artery, courses through the left atrio-ventricular groove giving off marginal branches that supply most of the left atrium, posterior and lateral free walls of the left ventricle. It also supplies the posterior papillary muscle of the mitral valve. It usually ends as an obtuse marginal branch but 15% of people have a left dominant circulation in which it supplies the posterior descending artery.

- ***Coronary Artery Dominance:***

Most people (approximately 65%) are *right* dominant, meaning that the posterior descending artery arises from the right coronary artery. About 15% of people are *left* dominant meaning that the posterior circumflex artery arises from the left circumflex artery. In about 20% of people, the area supplied by the posterior descending artery is supplied by branches from the right coronary and the circumflex branch of the left coronary artery, this is known as the *co-dominance* ***(Fuster et al., 2001)***.

Chapter 2
HISTOLOGICAL BACKGROUND

Structure of the heart wall: (Figure 3)

The wall of the heart is composed of three basic layers: the pericardium, the myocardium, and the endocardium.

The pericardium:

It consists of a *fibrous* (parietal) and a *serous* (visceral) sac. The **fibrous** pericardium is composed of collagenous fibrous tissue with an inner thin layer of mesothelial cells. The **serous** pericardium (also called the epicardium of the heart) is a single layer of mesothelium; containing variable amounts of adipose tissue within which are embedded the coronary arteries and veins, lymphatic vessels, nerves, fibroblasts, and macrophages ***(Berry and Billingham, 2007)***.

The myocardium:

It is the middle layer of the heart wall, thicker in the ventricles, made up of continuous wrapping of cardiac muscles forming concentrically-arranged layers around the chambers. Loose C.T. holds bundles of cardiac muscle fibers and contains numerous blood vessels ***(Young et al., 2006).***

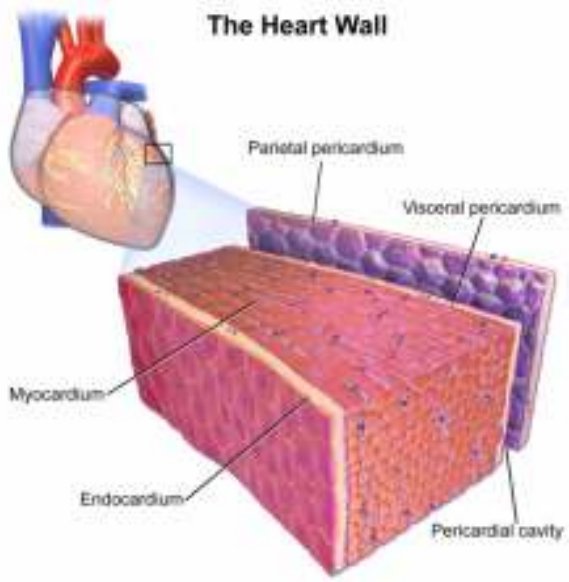

Figure (3): Structure of the heart wall ***(Wikipedia, 2013).***

The endocardium:

It represents the tunica intima of the heart, consisting of a lining layer of squamous endothelium underlied by a thin layer of loose C.T. with some smooth muscle cells and a deep sub-endothelial layer of C.T. ***(Young et al., 2006).***

Histology of Coronary Vessels:

Coronary artery (Figure 4) like any other artery, consists of three layers. The **tunica intima** which is the innermost layer, consists of a very thin lining of simple squamous endothelial cells supported by a thin layer of connective tissue and a prominent internal elastic layer (IEL) that separates it from the smooth muscle layer and collagen fibers of the **tunica media.** The outer most layer is the

adventitial layer which is relatively thick and contains collagen and elastic fibers, scattered fibroblasts, blood vessels and some adipose cells ***(Slomianka, 2009).***

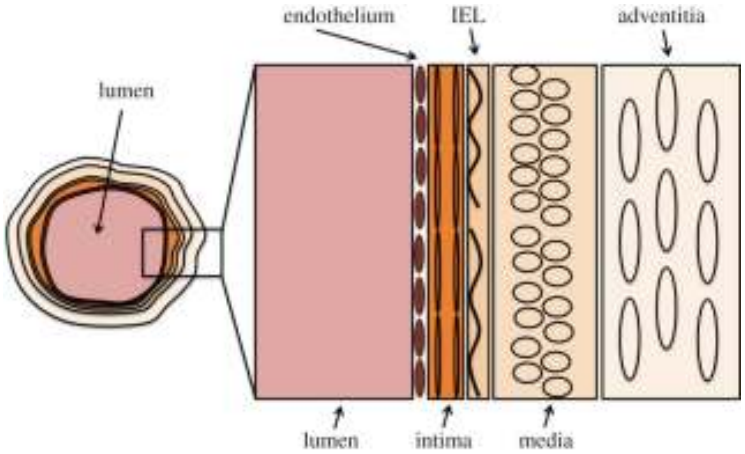

Figure (4): Structure of arterial wall ***(Kenjeres and Loor, 2013).***

Coronary veins have an endothelial layer that sits on an indistinct condensation of elastic fibers that produce a thin discontinuous internal elastic lamina. Together these three components comprise the inner layer of the vein. The outer layers, the tunica media and adventitia, vary considerably in thickness due to the proportions of collagen fibers, elastic fibers and smooth muscle present within them ***(Stevens and Lowe, 2004).***

Chapter 3
ATHEROSCLEROSIS

Diseases of the cardiovascular system are the leading cause of mortality and morbidity in developed countries. Despite modern medicine and interventions targeted towards ameliorating the problem, the prevalence of cardiovascular diseases has not only decreased in the past decades but, indeed, has drastically increased. Thus our need to understand the underlying patho-physiology and risk factors behind the development of cardiovascular diseases, in order to better manage them, has become ever more necessary and urgent. Among different cardiovascular diseases, "*atherosclerosis"* is a major contributing factor in the causation of ischaemic events ***(Wollard and Chin-Dusting, 2006).***

Atherosclerosis (also known as arteriosclerotic vascular disease or ASVD) is a condition in which an artery wall thickens as a result of the accumulation of fatty materials such as cholesterol and triglycerides. It is a chronic inflammatory response in the walls of arteries, caused largely by the accumulation of macrophages and white blood cells; and promoted by low-density lipoproteins (LDL) without adequate removal of fats and cholesterol from the macrophages by the high-density lipoproteins (HDL) ***(Hopkins et al., 1993).***

The following terms are similar, yet distinct, in both spelling and meaning, and can be easily confused ***(Gotlieb and Silver, 2001; Wikipedia, 2013).***

- *Arteriosclerosis* is a general term describing any hardening (and loss of elasticity) of medium or large arteries (from Greek ἀρτηρία *(artēria)*, meaning "artery", and σκλήρωσις *(sklerosis)*, meaning "hardening"). It is a degenerative disease of arteries including Monckberg Medial Calcific Sclerosis.
- *Arteriolosclerosis* is any hardening (with loss of elasticity) of arterioles. They show intimal and medial hyperplasia, hypertrophy, and fibrosis in such conditions as systemic hypertension and diabetes mellitus.
- *Atherosclerosis* is hardening of an artery specifically due to an atheromatous plaque. Around (1860), Felix J. Marchand (1846-1928) stated the term 'atherosclerosis' to emphasize the pathological findings of atheroma (Geek, hard) seen in intimal layers of the arteries ***(Aschoff, 1908)***. The term *atherogenic* is used for substances or processes that cause atherosclerosis. The main arteries affected by atherosclerosis are the aorta, and the coronary, cerebral, and popliteal arteries ***(Gotlieb and Silver, 2001).***

Atherosclerosis can be seen in the venous system in sites like the vena cava at its junction with the common iliac veins.